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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TUNGATURTHI, PARITHOSH K	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,148	SAWYER ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1,16 and 20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-15, 18 and 19, drawn to a method of producing a monoclonal antibody in the reply filed on 09/11/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

2. Claims 16 and 20-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

3. Claims 1-15, 18 and 19 are under examination.

Claim Objections

4. Claim 1 objected to because of the following informalities: Claim 1(e) recites "selecting as said monoclonal antibody".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are not clear for reciting "antigen being derived from a different source", because the exact meaning of the phrase is not understood. First, What does the applicant mean by derived? It is not clear if the term means a thought process or a design process. Does the term mean the antigen is prepared or engineer? Additionally, it is not clear if the term is to encompass recombinant methods as well as chemical modification. Second, the meaning of different source is unclear. What different sources is the applicant refereeing to? The phrase "different source" can be interpreted as "an antigen that is a protein obtained from different parts of the body to an various immunogenic epitopes selected from the same antigen or protein? The inclusion of such phraseology in the claim without any clear indication renders the claim confusing. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

Appropriate correction is require.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kucherlapati et al (US Patent 6150584; Date Issued: 11/21/2000).

The instant claims are drawn to a method for producing a monoclonal antibody, said method comprising the steps of: a) introducing at least one candidate antigen into an animal; b) recovering antibody-producing cells from said animal and rendering these cells into a single cell suspension; c) generating an immortalized cell line from said single cell suspension; d) screening the supernatant of said immortalized cell line against a protein chip on which the candidate antigen is displayed; and (e) selecting as said monoclonal antibody, an antibody that binds to said candidate antigen; wherein said animal is a mouse, a rat, a guinea pig or a rabbit; wherein said candidate antigen is a purified candidate antigen; wherein between one and fifty different purified candidate antigens are introduced into the ; wherein between 0.001 and 1000 micrograms of each antigen is introduced into the animal. Further, the claims are drawn to a method of claim 1 comprising the additional step of supplying the animal with a booster dose of some or all of the antigens which were introduced into the animal prior to the removal of antibody-producing cells, wherein the antibody-producing cells are B cells, T cell or stem cells, wherein the antibody-producing cells are recovered by removal of spleen tissue, lymph nodes or bone marrow of the animal, wherein the immortalized cell line is a hybridoma cell line produced by somatic fusion of the cells in the single cell suspension to myeloma cells.

Kucherlapati et al teach (abstract and paragraph 18, in particular) a method of producing monoclonal antibodies comprising administering the antigen into a nonhuman

animal (mouse, in this instance), obtaining B cells, typically from the spleen, but also, if desired, from the peripheral blood lymphocytes or lymph nodes and immortalizing using any of a variety of techniques; and culturing the resulting hybridomas or otherwise immortalized B cells and screen for the secretion of antibodies of the desired specificity. In Example 1, Kucherlapati et al teach that 50 micrograms of the antigen (human IL-6, in this instance) was used for immunizing the mouse intraperitoneally. Kucherlapati et al also teach preparation of high affinity human monoclonal antibodies (example 9, paragraphs 120-123, in particular), wherein the antibodies were screened for their kinetic parameters, specifically their on and off rates and their dissociation constants (Kd) by BIAcore instrument which uses plasmon resonance to measure the binding of an antibody to an antigen-coated gold chip. Kucherlapati et al also teach (paragraph 5, in particular) that it may be necessary to provide the antigen with a carrier to enhance its immunogenicity and/or to include formulations which contain adjuvants and/or to administer multiple injections and/or to vary the route of the immunization, and the like.

Thus, since Kucherlapari et el teach the method for producing at least one monoclonal antibody comprising introducing at least one candidate antigen into a non-human animal ..... and selecting the said monoclonal antibody as claimed, Kucherlapati et al read on the instant claims.

Hence Kucherlapati et al anticipate claims 1-9 and 13.

8. Claims 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Mather et al (WO/2000/037503; Publication Date: 06/29/2000).

The Instant claims are drawn to a method for producing a plurality of monoclonal antibodies, each of which binds to a different purified candidate antigen, comprising introducing a plurality of purified candidate antigens into an animal, each purified candidate antigen being derived from a different source; and a method for producing a plurality of monoclonal antibodies, each of which binds to a different purified candidate antigen comprising introducing a plurality of purified candidate antigens into an animal, each purified candidate antigen being derived from a different source, which further comprises any of the steps recited claim 1.

Mather et al (Summary of the Invention and example 2, in particular) teach a method of generation of a population of monoclonal antibodies capable of binding to antigens, especially cell surface antigens. Mather et al teach a method for immunizing a host mammal to produce a population of monoclonal antibodies that bind to antigens representative of a specific cell type that are heterologous to the host mammal; wherein the method comprises introducing into the mammal a plurality of viable and intact cells of said cell type, wherein the surfaces of the cells are free of serum. Mather et al also teach a method of generating monoclonal antibodies binding to the surface antigens of a specific cell type, which involved (a) immunizing a host mammal with a plurality of viable and intact cells of a specific cell type that are heterologous to the host mammal, wherein the surfaces of the cells are free of serum; (b) fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that produce monoclonal antibodies; (c) culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; and (d) selecting the hybridomas that secrete

monoclonal antibodies binding to surface antigens present on the viable and intact cells used for immunization. In addition, please see the definitions of "A population of monoclonal antibodies" and "surface antigens" as described by Mather et al.

Thus, since Mather et al teach a method for producing a plurality of monoclonal antibodies comprising introducing into the mammal a plurality of viable and intact cells of said cell type for generating monoclonal antibodies that to the surface antigens of a specific cell type, in addition to selecting the hybridomas that secrete monoclonal antibodies binding to specific surface antigens, Mather et al read on claims 18 and 19.

Hence, Mather et al anticipate the instant claims 18 and 19.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-15, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al (US Patent 6150584; Date Issued: 11/21/2000) in view of Mather et al (WO/2000/037503; Publication Date: 06/29/2000) in view of Rava et al (US Patent 6720149; Date Filed 05/28/2002, Claims priority to 10/10/1999) in view of Kessler et al (PGPUB 20030044849; Date Filed:08/21/2002, Claims priority to 10/22/2001).

Claims 1-9, 13, 18 and 19 have been described supra. Claims 10-12 are draw to the method of claim 1, wherein said protein chip is a plain-glass slide, a 3D gel pad chip, a microwell chip or a cell chip, wherein the step of detecting the monoclonal antibodies bound to the antigens further comprises isotyping the monoclonal antibodies, wherein said step of detecting and isotyping the monoclonal antibodies comprises adding isotype specific anti-immunoglobulin antibodies to said protein chip, wherein each anti-immunoglobulin antibody having a different isotype specificity has a different label, and detecting the presence of said labels. Further claims 14 and 15 are drawn to a high-throughput method for producing a plurality of monoclonal antibodies, each of which binds to a different candidate antigen, comprising the steps of: a) introducing a plurality of candidate antigens into an animal; b) recovering antibody-producing cells from said animal and rendering these cells into a single cell suspension; c) generating immortalized cell lines from said single cell suspension; d) screening the supernatant of said immortalized cell lines against one or more protein chips on which the candidate

antigens are displayed; and e) selecting as said monoclonal antibodies, antibodies that bind to said candidate antigens, which further comprises any steps recited in claim 1.

Kucherlapati et al has been described supra. Kurlapati et al does note teach a method for producing a plurality of monoclonal antibodies and isotyping of monoclonal antibodies. These deficiencies are made up for my Mather et al, Rava et al and Kessler et al.

Mather et al have been described supra.

Rava et al teach methods for concurrently processing multiple biological chip assays by providing a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe array; introducing samples into the test wells; subjecting the biological chip plate to manipulation by a fluid handling device that automatically performs steps to carry out reactions between target molecules in the samples and probes; and subjecting the biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules and probes (abstract, in particular). Rava et al teach that a probe can be selected from proteins of interest and the targets can be selected from monoclonal antibodies and the antisera reactive with specific antigenic determinants (detailed description, paragraph 3; in particular). Rava et al defines a chip as a substrate, which can be silicon or glass, having a surface to which one or more arrays of probes is attached.

Kessler et al teach that can antibodies manipulated based on antigenic or structural markers on the immunoglobulins of different animal species, classes or isotypes, subclasses, allotypes. For example, human monoclonal antibodies being screened may be distinguished from a PAL consisting of murine antibodies by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-human immunoglobulin reagents. Other usable labels besides fluorescers and enzymes include radiosiotopes, chemiluminescers, phosphors, particles, etc. In addition, measurements of affinities, avidities, association rates or dissociation rates can be made directly or indirectly on the monoclonal antibodies by surface plasmon resonance (e.g., BIAcore).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used alpha 2-HS glycoprotein, a human homolog of bovine fetuin, as taught by Chan et al, to induce apoptosis in cancer cells where in the cancer cells are prostate cancer cells as taught by Tsai and Yu (U.S. '298) at a dosage of about 10 mg/kg body weight as taught by Tsai and Yu (U.S. '779).

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced a monoclonal antibody as claimed in claims 1-9, because Kucherlapati et al teach a method of producing monoclonal antibodies comprising administering the antigen (50 micrograms, in this instance) into a

mouse, obtaining B cells from the spleen and immortalizing and culturing the resulting hybridomas; and screen for the secretion of antibodies of the desired specificity by BIAcore instrument which uses plasmon resonance to measure the binding of an antibody to an antigen-coated gold chip; in addition to teaching that it may be necessary to administer multiple injections of the antigen with to enhance its immunogenicity.

In addition, one of ordinary skill in the art would have known to combine the teachings of Kucherlapati et al and Mather et al, because Kucherlapati et al teach a method of producing monoclonal antibodies comprising administering the antigen into a mouse and because Mather et al teach a method of generation of a population of monoclonal antibodies capable of binding to antigens, especially cell surface antigens by immunizing a host mammal (for example, rat); wherein the method comprises introducing into the mammal a plurality of viable and intact cells of said cell type (presenting the various cell surface markers as different antigens to produce a plurality of antibodies), wherein the surfaces of the cells are free of serum. Mather et al also teach a method of generating monoclonal antibodies binding to the surface antigens of a specific cell type, which involved (a) immunizing a host mammal with a plurality of viable and intact cells of a specific cell type (which presents various cell surface markers as different antigens to produce a plurality of antibodies) that are heterologous to the host mammal, (b) fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that produce monoclonal antibodies; (c) culturing the hybridomas under the ,conditions favorable for the secretion of monoclonal

antibodies, and (d) selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells used for immunization.

Further, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the above teachings with Rava et al and Kessler et al because Rava et al teach methods for concurrently processing multiple biological chip assays by providing a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe (which can be selected from proteins of interest, for example) array; introducing samples into the test wells; subjecting the biological chip plate to manipulation by a fluid handling device that automatically performs steps to carry out reactions between target molecules (which can be selected from monoclonal antibodies, for example) in the samples and probes; and subjecting the biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules; and further because Kessler et al teach that antibodies can manipulated based on antigenic or structural markers on the immunoglobulins, for example various isotypes can be generated; in addition to teaching that human monoclonal antibodies can be distinguished by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-human immunoglobulin reagents, including other usable labels besides fluorescers and enzymes include radiosiotopes, chemiluminescers, phosphors, particles, etc.

Thus, it would have been obvious to one of ordinary skill in the art one would have been motivated to produce the claimed invention because Kucherlapati et al teach

a method of producing monoclonal antibodies comprising administering the antigen in addition that the antibodies were screened for their kinetic parameters using the BIAcore instrument, and because Mather et al teach a method of generation of a population of monoclonal antibodies capable of binding to antigens, especially cell surface antigens by immunizing a host mammal by immunizing the mammal with a plurality of viable and intact cells of said cell type (presenting the various cell surface markers as different antigens to produce a plurality of antibodies), and because Rava et al teach methods to carry out reactions between target molecules in the samples and probes wherein a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe array is provided to which the sampled to be screened are introducing and biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules and probes, and further because Kessler et al teach that isotypes of various antibodies can be generated and screened, by surface plasmon resonance (e.g., BIAcore) which used the protein-chip technique, by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-human immunoglobulin reagents, such as labels besides fluorescers and enzymes including radiosiotopes, chemiluminescers, phosphors, particles, etc. In addition, measurements of affinities, avidities, association rates or dissociation rates can be made directly or indirectly on the monoclonal antibodies).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Cao et al. 1991. Biotechniques 10(5):574-578. (Abstract Included) – teach the development of a method of subclass isotyping and screening for monoclonal antibodies , wherein the monoclonal antibodies against Mycoplasma gallisepticum were screened and isotyped in using this technique.

Conclusion

13. No claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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SHEELA HUFF
PRIMARY EXAMINER